Remarks/Arguments:

A. Status of the Claims

Claims 1-19, 29-30, 32-34, and 36-40 were pending when the Office Action was mailed to Applicants. Claims 1, 3-4, 8, 13, 15-19, 33, and 37 have been amended and claims 2, 6-7, 14, 32, 36, and 39-40 have been canceled. Support for the amendments can be found throughout the specification and claims as originally filed. Claims 1, 3-5, 8-13, 15-19, 29-31, 33-34, and 37-38 are therefore currently pending.

B. The Written Description Rejection Is Rendered Moot

Claims 39 and 40[1] are rejected under 36 U.S.C. § 112, first paragraph, for lack of written description.

Applicants disagree. The specification provides the appropriate written description for these claims. For example, see page 38 of the specification. However, in an effort to further the prosecution in this case, and to obtain commercially relevant claims at this time, claims 39 and 40 have been canceled.

Applicants request that the present written description rejection be withdrawn.

C. The Enablement Rejection Is Overcome

Claims 1-19 and 29-30, 32-34, and 36-40 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. According to the examiner, the claims are not enabled for practicing of the invention as broadly claim, but instead, are enabled only to the extent of:

(i) using a biotin-liposome complex;

(ii) using avidin as an anti-ligand; and

[1] The Action lists claims 1, 39, and 40 as being rejected for lack of written description. Applicants will treat this rejection as only applying to claims 39 and 40 in view of the examiner's statement that "[t]his rejection is mainly applied to the claimed embodiments as set forth in claims 39 and 40." Page 3 of the Action.

(iii) subcutaneous administration, wherein the avidin is injected at the same site or adjacent to the site the biotin is injected.

The Action, pages 4-5. The examiner further contends that claims 32 and 36 should be canceled because the specification does not provide enablement for "liposomal particles having a size of 5 nm."

Applicants disagree. The claims prior to the amendments made above are enabled by the specification. The pending claims also satisfy the requirement under 35 U.S.C § 112, first paragraph.

Applicants note that the pending claims are currently directed towards a biotin-liposome complex and the use of avidin as an anti-ligand. Additionally, claims 32 and 36 have been canceled at this time. Therefore, the only issue remaining is whether the claims should be limited to subcutaneous administration, wherein the avidin is injected at the same site or adjacent to the biotin-liposome complex injection site, and *vice versa*.

1. The Pending Claims Meet the Enablement Standard

The examiner has the initial burden to establish a reasonable basis to question the enablement of the claimed invention. See MPEP § 2164.04. Only if an examiner can provide reasons sufficient to create a reasonable doubt as to the accuracy of a particular broad statement put forward by applicant as enabling support for a claim, a rejection under 35 U.S.C. §112, first paragraph, can be made. In other words, a specification which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling

support. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971). With that framework in mind, applicants address the Examiner's non-enablement position.

2. The Specification Is Enabled For Subcutaneous and Other Routes of Administration

The Examiner contends that the specification provides enablement only to the extent that subcutaneous administration is used. In essence, the Examiner is attempting to limit the present claims to a particular route of administration (subcutaneous) at the exclusion of other known routes of administration, including those disclosed in the specification. This is improper in view of Applicants' specification, the Declaration of Beth A. Goins ("Goins Declaration") (Appendix A) and U.S. patent law.

The specification discloses several different non-limiting routes of administration that can be used in the context of the present invention. See, for example, page 14, lines 14-22. It cannot be disputed (and the Examiner has provided no evidence to the contrary) that administering compositions *via* these exemplary routes is routine in the art and does not require undue experimentation. The Goins Declaration confirms this:

> Based on my knowledge and experience in the field of drug delivery, a person knowledgeable in drug delivery, by following the disclosure in the specification, would be capable of using subcutaneous and other routes of administrations such as those disclosed at page 14, lines 14-17, of the specification to practice the claimed invention without undue experimentation.
>
> The specification describes how one would administer a first composition comprising a biotin-liposome complex and a second composition comprising an avidin. For example, page 14, lines 14-17, of the specification provide examples of the different types of administration routes that can be used. Administering the first and second compositions to a subject *via* these exemplary routes is routine in the drug delivery field and would not require undue experimentation.

Goins Declaration, ¶¶ 4-5; see also MPEP § 2164.01(b) (noting "[i]f a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied.").

Further, as noted by Dr. Goins, "...the specification provides data showing the delivery and retention of liposomes in one or more targeted lymph nodes when practicing the claimed invention *via* subcutaneous, submucosal, and intraperitoneal administration. Examples 12-15 for instance, are directed towards subcutaneous administration, Example 18 concerns intraperitoneal administration, and Example 19 concerns submucosal administration." *Id.* at ¶ 6.

Applicants also note that several other references confirm that other routes of administration can be used to deliver and retain liposomes in one or more targeted lymph. This is explained by Dr. Goins:

> Published references also confirm that other routes of administration (*i.e.*, other than subcutaneous) can be used to deliver and retain liposomes in one or more targeted lymph nodes when practicing the claimed invention. These references use biotin-liposome complexes in combination with avidin. The references provide data showing the delivery and retention of the biotin-liposome complexes in one or more targeted lymph nodes *via* intrapleural and intraperitoneal administration:
>
> (i) Phillips *et al.*, *J. of Pharmacology and Experimental Therapeutics*, 303(1):11-16 (2002) (Appendix 2). The Abstract in Phillips *et al.* provides:
>
> > An aliquot (1 ml) of technetium-99m (^{99m}Tc)-biotin-liposomes encapsulating blue dye was injected intraperitoneally in rats. Thirty minutes after administration of the ^{99m}Tc-biotin-liposomes, five rats (experimental) were administered avidin (5 mg) intraperitoneally, whereas the remaining five rats served as controls...Significant ^{99m}Tc activity was detected in blue-stained abdominal nodes (4.7%) and mediastinal nodes (2.3%) from the experimental animals, whereas no blue-stained nodes were detectable in the control animals.
>
> (ii) Medina *et al.*, *J. of Pharmaceutical Sciences*, 93(10):2595-2608 (2004) (Appendix 3). The Abstract in Medina *et al.* provides:

> The objective of this study was to develop a more effective liposome-based method for delivering drugs to mediastinal nodes. Nodal uptake was determined after intrapleural injection of the avidin/biotin-liposome system in normal rats. The effect of injection sequence (avidin injected 2 h before biotin-liposomes and vice versa), volume injected, and administered dose of the agents is described...When avidin was injected before ^{99m}Tc-biotin-liposomes, better mediastinal node targeting (15.7%; $p<0.05$) was achieved than when biotin-liposomes were injected first (8.3%) or when only biotin-liposomes were injected (1.0%).

Id. at ¶ 7.

The above information is overwhelming evidence that the specification is enabled for subcutaneous and other routes of administration such as those listed on page 14, lines 14-17 of Applicants' specification. *Id* at ¶ 4. U.S. patent law confirms this. See MPEP § 2164.02 (noting "[f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinary be sufficient if one skilled in the art...would expect the claimed genus could be used in that manner without undue experimentation."); see also *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) (holding that claims to a generic class of antibodies are enabled where applicant made a public deposit of only a single hybridoma cell line that secreted a specific antibody); *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) (noting that "[i]t is well settled that patent applicants are not required to disclose every species encompassed by their claims....").

Therefore, the Examiner's attempt to limit the present claims to a particular route of administration (subcutaneous) is improper. Applicants request reconsideration and withdrawal of this aspect of the enablement rejection.

3. The Specification Is Enabled For Same Site, Adjacent Site, and Non-Adjacent Site Administration

The Examiner contends that the specification provides enablement only to the extent that avidin is injected at the same site or adjacent to the biotin-liposome complex injection site, and

vice versa. This too is improper in view of Applicants' specification, the Goins Declaration, and U.S. patent law.

As noted by Dr. Goins, "[a] person knowledgeable in drug delivery, by following the disclosure in the specification, would be capable of injecting the avidin containing composition at the same site, an adjacent site, or a non-adjacent site to the biotin-liposome injection site, and *vice versa*, without undue experimentation." Goins Declaration, ¶ 8. The specification, in fact, provides data confirming this:

> For instance, in the subcutaneous administration data of Examples 12-15 of the specification, avidin was injected approximately 2 cm proximal to the biotin-liposome injection site. With respect to the submucosal administration data in Example 19, avidin was injected approximately 5 cm distal to the biotin-liposome injection site. These data show that the avidin and biotin-liposome containing compositions can be injected at non-adjacent sites.

Id. at ¶ 9.

Further, Dr. Goins provides additional data obtained from an experiment described in paragraphs 10-13 of her Declaration. In summary, the experimental set-up included injecting one component, either avidin or biotin-liposomes, into the peritoneal cavity and the corresponding component into the pleural space. Paragraph 14 of the Goins Declaration summarizes the results of the experiment:

> The results of the four experimental and four control groups show that when no avidin is injected, liposomes leave the injection site (either pleural space or abdominal cavity), move into blood circulation and eventually collect in spleen and liver with minimal accumulation in mediastinal nodes or collecting lymphatics. However, when avidin is injected, accumulation in mediastinal nodes, diaphragm, and collecting lymphatics in the pleura that cover the diaphragm is observed. Table 1 at Appendix 4 provides a summary of these data. Further, these data confirm that the avidin and biotin-liposome containing compositions can be administered at different and non-adjacent sites.

Id. at ¶ 14.

The above evidence confirms that Applicants' specification provides enablement for injecting avidin at the same site, an adjacent site, or a non-adjacent site to the biotin-liposome injection site, and *vice versa*, without undue experimentation. Applicants therefore request reconsideration and withdrawal of this aspect of the enablement rejection.

D. Conclusion

Applicants believe that the present document is a full and complete response to the Office Action dated June 29, 2005.

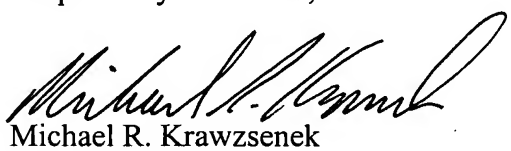
III. A Petition for a One-Month Extension of Time:

Pursuant to 37 C.F.R. § 1.136(a), Applicants petition for an extension of time of one month to and including October 29, 2005, in which to respond to the Office Action dated June 29, 2005. Because October 29 falls on a Saturday, the due date is extended to Monday, October 31 pursuant to 37 C.F.R. § 1.7.

A check in the amount of $60.00 is enclosed, which is the process fee for a one-month extension of time for a small entity status. If the check is inadvertently omitted, or should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an overpayment be included herein, the Commissioner is authorized to deduct or credit said fees from or to Fulbright & Jaworski Deposit Account No. 50-1212/UTSK:343US.

The Examiner is invited to contact the undersigned Attorney at (512) 536-3020 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



Michael R. Krawzsenek
Reg. No. 51,898
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 536-3020

Date: October 31, 2005